ALKYLATION OF THE AMBIDENT FORMANILIDE ANION

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ALKYLATION OF THE AMBIDENT FORMANILIDE ANION

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ABSTRACT

Benzylation of lithium, potassium, tetraethylammonium and silver salts of the ambident formanilide anion under different reaction conditions has been studied.

The lithium, potassium and tetraethylammonium salts generally gave exclusively N-benzylation whereas the reaction with silver salts occurred predominantly on oxygen. The choice of solvent, the halide of the benzyl halide, and the substituent on the alkylating agent and/or formanilide did not affect the site of alkylation of the alkali metal salts but the oxygen and nitrogen alkylation product distribution from the silver salt alkylations did depend, to some extent, upon these factors. The highest O-alkylation in the case of the silver salt was always obtained in dimethoxyethane, while the reaction in dimethylformamide gave comparatively high yields of N-alkylation product. Exceptional cases are reported where N-alkylation was predominate in silver salt alkylations and these will be discussed.

A number of formiminoalkyl ethers and N-alkylformanilides were isolated and their spectra are compared.

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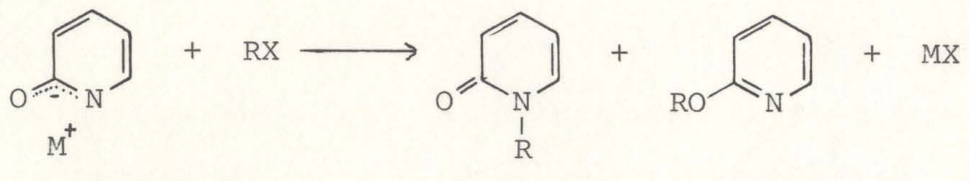
INTRODUCTION

The term "ambident anion" has been used by Kornblum (1) for the anion systems containing two centers susceptible to electrophilic attack, but in which only one of these centers can take part in a single transition state. Extensive studies have been concentrated on alkylations of enolate (2) and phenoxide anions (3). Other ambident anions that have been alkylated include the cyanide (4), pyrryl (5) and nitrite (6) anions and the salts of oximes (7), pyrimidines (8), pyridones (8), amides and so on.

Systematic investigations carried out over the past few years have revealed that the relative proportions of products resulting from the two possible reaction paths depend on numerous factors. Indeed, the site of alkylation of ambident anions can generally be controlled by conducting the reaction under different conditions. Factors such as medium, metal counter ion, leaving group, structure of the alkylating agent and substrate, etc. which usually lead to different product distributions have long been studied and are well reviewed (9).

While the problems of alkylations of most ambident anions may now be regarded as being largely clarified, the same can not be said of the behavior of amide anions although a number of studies have been done (10). Systematic studies on the alkylation of ambident anions analogous to amide ions

are only found in the work by G. C. Hopkins and coworkers (8). They report that the sites of alkylation of pyrimidine and pyridone salts are influenced by the variation of metal counter ion, solvent, alkylating agent, substituent on the substrate and the reaction conditions. Of the pyrimidine and pyridone ambident anions, the latter is more closely related to our work so that brief review of effects on its alkylation reaction follows. It is well known that the reaction of a 2-pyridone salt with an alkyl halide can give a 2-alkoxypyridine as well as an N-alkyl-2-pyridone (Eqn. 1).



(Eqn. 1)

Oxygen alkylation is favored in the reaction of the silver salt in nonpolar solvents such as benzene, hexane and pentane and was ascribed to the result of an heterogeneous reaction specific to the silver salt. In the better ion-solvating solvents such as dimethylformamide (DMF), dimethoxyethane (DME), etc., more reaction can take place in solution and N-alkylation of the silver salt is increased. The effect is more pronounced with silver salt of 5-carbethoxypyridone, which gives 96% N-alkylation in DMF and only 2% when hexane is used.

The reaction of lithium, sodium, and potassium salts of 2-pyridone always occurs on nitrogen. Oxygen alkylation becomes more important when DMF is used as the solvent. This is observed in the reaction of the sodium salt of 2-pyridone where charge separation of the ion-pair is enhanced by the high dielectric constant of the medium.

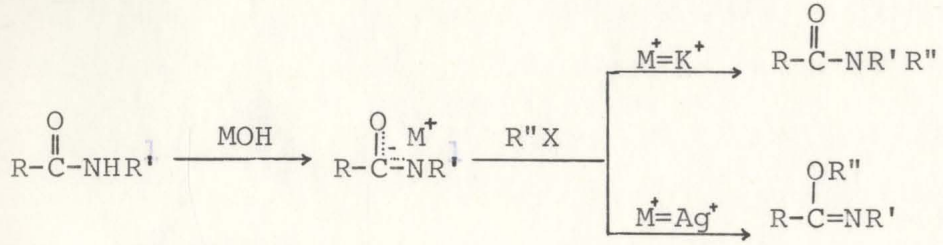
The steric effect in the alkylation of 2-pyridone salts results in an increase in ether formation when the alkylating agent is changed from methyl to ethyl to isopropyl halide. This demonstrates that N-alkylation has a greater steric requirement than does O-alkylation.

Substituents on the pyridone ring can also affect the product distribution, electron-withdrawing groups such as carbethoxy- or nitro- on the 5-position of 2-pyridone causes increased N-alkylation.

In the alkylation of an amide anion, an N-alkylated amide and an O-substituted product, an imino-ether, are formed. Factors that influence the product distribution in the alkylation of 2-pyridone salts would be expected to influence the product distribution in the alkylation of amide salts since the two anion systems are structurally similar.

A review of the literature (10) has shown that not all these effects are always observable because too often reaction at one site is strongly favored over another simply by the effect of a certain cation, a certain type of alkylating

agent or other special factors such as steric effects. Thus, primary and secondary amides in the presence of a strong base, normally react at the nitrogen atom (11) (Eqn. 2). Predominantly O-alkylated products are obtained, however, in the presence of silver salts (12) (Eqn. 2).



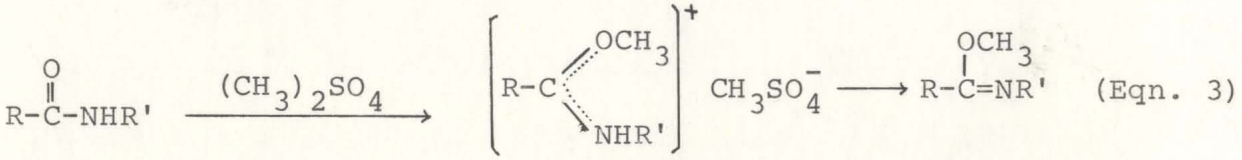
(Eqn. 2)

Kornblum (1) attributed the tendency towards either O- or N-alkylation of ambident anions (including amide anions) to the nature of the transition state. He states that for reactions with "S_N1-like" transition states, alkylation of the more electronegative oxygen atom is favored, whereas greater S_N2 character in the transition state favors alkylation of the less electronegative nitrogen atom. Silver salts are supposed to enhance the unimolecular nature of the reaction by polarization of the alkyl halide bond, thereby promoting alkylation at oxygen.

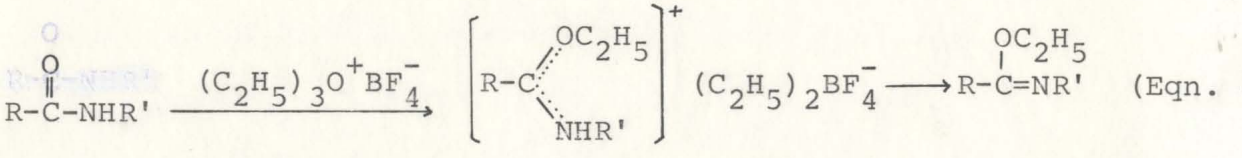
Other examples of alkylation of silver salts leading to O-alkylated products are found in the work by G. D. Lander (13). He was able to prepare a number of

imino-ethers by the action of dry silver oxide and ethyl iodide on acetanilide, benzanilide, etc.. Instead of utilizing silver oxide or adding silver salt to the alkali metal salt of the amide, alkylation can be carried out directly on the isolated silver salts of amides. Silver formanilide, for instance, has been used for the preparation of N-phenylformiminoalkyl ethers (14).

Alkylating agents such as dialkyl sulfates, trialkyloxonium tetrafluoroborates(15), ethyl chloroformate (16) and diazoalkanes (17) can also lead to O-alkylations. Dialkyl sulfates and trialkyloxonium tetrafluoroborates (15) react with primary or secondary amides to give the corresponding O-alkylimidonium salt, from which the imino-ether can be recovered (Eqns. 3, 4).



(Eqn. 3)



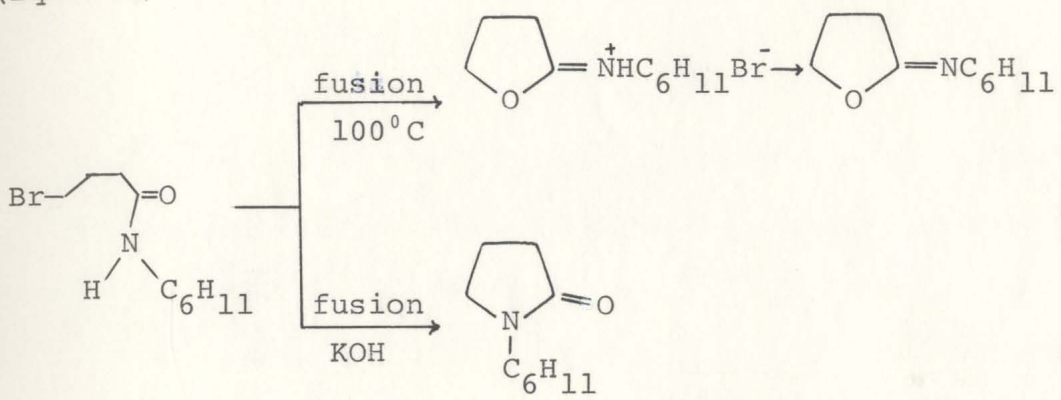
(Eqn. 4

Alkylation by diazoalkanes is known to give a mixture of O- and N-alkylated products. Oxygen substitution is favored by enhanced single-bond character of the carbonyl group and is related to increased delocalization of the nitrogen lone-pair electrons (17). This is evident from the studies with different types of amides (17).

While the O-alkylation product can be obtained from reaction of silver salt or with the use of dialkyl sulfate, oxonium salt and etc., alkylation of primary and secondary amides with alkyl halides in the presence of such bases as sodium alkoxide, sodium hydride or sodamide always occurs on the nitrogen and this is regarded as the most satisfactory way of synthesizing more highly substituted amides. These reactions are well documented and details can be found elsewhere (10).

Examples of O- and N-alkylation resulting from intramolecular reaction are also known and the site of alkylation is reported to depend upon experimental conditions (18) Nitrogen substitution predominates in strongly alkaline conditions in which the anion of the amide is present, whereas, in neutral solutions, only the products of O-substitution are normally observed. For example, cyclisation of 4- bromo-N-cyclohexylbutyramide (I) in neutral conditions occurs by displacement of the halide ion by the carbonyl oxygen of the amido-group (Eqn. 5a), while in basic conditions,

a proton is presumably lost from the amido-nitrogen atom and cyclisation gives an N-substituted pyrrolid-2-one (16) (Eqn. 5b).



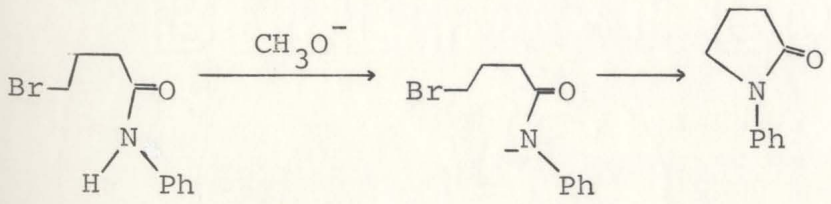
(Eqn. 5a)

(Eqn. 5b)

(I)

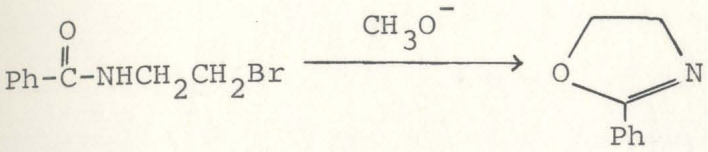
In this example there is no possibility that steric factors are involved because the cyclic products are of the same size. A corresponding O- to N-rearrangement should be prohibited by the energetics of ring opening.

Alkaline solvolysis of N-phenyl-4-bromobutamide (II) to form N-phenyl-pyrrolidone (III) also results from alkylation on nitrogen (19).



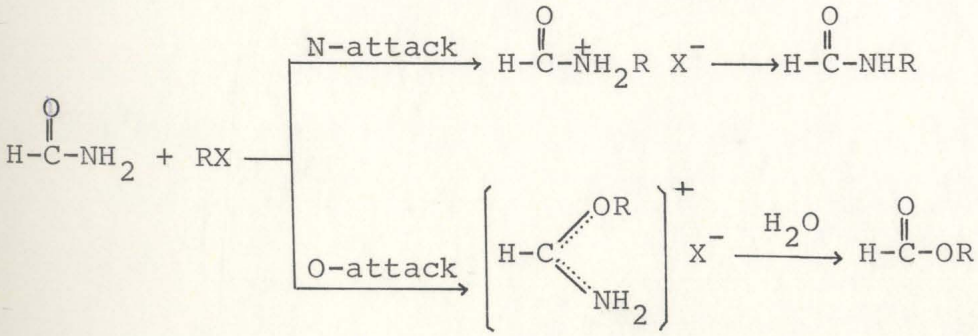
(II) (III)

In contrast to the previous case, the formation of 2-phenyl-oxazoline (V) from N-2-bromoethylbenzamide (IV) (20) under basic conditions probably indicates N-alkylation is sterically unfavorable.



(IV) (V)

Sometimes, alkylations are achieved by carrying out the reactions at elevated temperatures when the alkylating agents are less reactive and without the presence of bases to catalyze the reactions. Bredereck and his colleagues (21) have studied some alkylations on formamide at temperature as high as 150°C. No imino-ethers were isolated; instead, the alkyl formates were obtained from hydrolysis of the O-alkylated products (Eqn. 6).



(Eqn. 6)

With various alkylating agents, they found that usually N-alkylformamides (i.e. N-substitution) are favored with alkyl halides forming relatively stable carbonium ions (e.g. Ph_3CCl, Ph_2CHCl), whereas less polarizable reagents such as benzyl chloride and n-octyl bromide, preferentially form the alkyl formate. All these reactions show

pseudo-first-order kinetics and the rate is increased when the developing alkyl carbonium ion is more stabilised. However, the S_N1 character in formamide alkylations is not in line with substitution on oxygen, which is the atom of higher electronegativity. This fact apparently disagrees with Kornblum's (1) prediction although some N-alkylated product can possibly result from thermal rearrangement of the O-isomer.

We report here some studies on the alkylation of lithium, potassium, and silver salts of formanilide, p-methoxy-, p-bromo-, and p-nitroformanilide in hexane, toluene, DME and DMF with benzyl halides as the alkylating agents. Alkylation of tetraethylammonium salt of formanilide in DMF has also been studied. Effects of changing the halide of the alkylating agent and of changing substituent on the benzyl halide were also examined. Some imino-ethers and N-benzylformanilides were isolated and their spectra compared.

RESULTS

Lithium and potassium salts of formanilide, p-methoxy-, p-bromoformanilides all gave N-alkylation products with benzyl bromide in hexane, toluene, DME and DMF (Table 5). Tetraethylammonium formanilide also gave solely N-alkylation product in DMF (p. 39). At room temperature, the lithium formanilides did not have any appreciable reaction with the benzyl bromide in hexane and toluene. The yields were usually below 10% even when the solutions were heated at reflux temperatures for 4 hours.

In DME, the reactions of lithium salts of the three formanilides were slow, but most of the salts were converted after refluxing the solutions from 15 minutes to 2 hours. In DMF, both lithium and potassium salts reacted immediately when the benzyl bromide was added.

Potassium salts were generally more reactive than the corresponding lithium salts, this probably correlates with their higher solubilities in solvents such as toluene, DME and DMF. Even in hexane, the potassium salts reacted fairly well without heating.

In general, yields ranging from 60% to over 90% were obtained from potassium salts in all solvents and from lithium salts in DME and DMF.

With benzyl iodide, the lithium salts in DMF and potassium salts in DME and DMF reacted smoothly at room

temperature to give over 80% of yield (Table 6). The reactions of the lithium salts in DME required heating to enhance the percentage of conversion. Potassium p-nitroformanilide also gave very high yield (over 90%) with benzyl iodide in DME, but the yield from DMF was comparatively low (Table 6). No O-alkylation was observed in any of these reactions.

Reactions of lithium and potassium formanilides with p-bromo-, p-nitro, p-methyl, p-methoxybenzyl bromide and p-methoxybenzyl chloride resulted high yields (over 70%) except in the case where p-nitrobenzyl bromide was the alkylating agent and DMF the solvent (Table 7). Again, no O-alkylation was detected.

Benzylations of the silver formanilides with various benzyl halides gave mixtures of N-benzylated formanilides and formimino-ethers. The starting formanilides were also found and proven to arise from hydrolysis of the formimino-ethers. The ratio of the amount of oxygen to nitrogen alkylation, the O/N ratios, were estimated for the alkylations of silver formanilides with different benzyl halides in different solvents and are listed in Table 1. Usually, with benzyl bromide as the alkylating agent, silver formanilides gave their highest O/N values in DME. In DMF, amounts of O- and N-alkylations were more nearly equal than in other solvents. O/N values for reactions in hexane and toluene were in between those from the reactions in DME and DMF.

Table 1. O/N values for reactions of silver formanilides with different benzyl halides in hexane, toluene, DME, DMF[a].

R_1[b]	R_2,	X[c]	Hexane	Toluene	DME	DMF
H	H	Br	8.0	8.3	16.3	1.4
H[d]	H	Br	16.7	23.4	33.0	4.4
H[d]	H	Br	14.3	-	21.5	6
CH_3O	H	Br	3.7	12.2	8.8	1.0
CH_3O[d]	H	Br	3.4	19.7	17.0	3.5
Br	H	Br	1.3	6.0	10.1	0.5
Br[d]	H	Br	4.4	8.0	13.5	1.0
H	H	I	0.1	0.2	20.4	1.3
CH_3O	H	I	0.4	0.6	4.2	0.8
Br	H	I	0	0.3	9.4	0.9
H	CH_3	Br	10.7	4.2	12.6	1.6
H	Br	Br	4.8	7.0	13.2	2.0
H	CH_3O	Cl	0	0	0	0
H	CH_3O	Br	0	0	0	0

a. The same batch of salt was used for the runs in a row, i.e. for all four solvents.

b. R_1 denotes the p-substituent of the formanilide.

c. R_2 and X denote the p-substituent and the halogen of the benzyl halide respectively.

d. Duplicate runs under similar reaction conditions.

With benzyl iodide, O/N values were mostly the same as with benzyl bromide in DME and DMF, except in hexane and toluene where N-alkylation always predominated.

Alkylations with p-bromo- and p-methylbenzyl bromide showed no differences from those reactions in which benzyl bromide was employed.

Extraordinarily, p-methoxybenzyl bromide and chloride gave exclusively N-alkylation products with the silver salts (Table 10). The yields were lower than those from the reactions for the corresponding lithium and potassium salts.

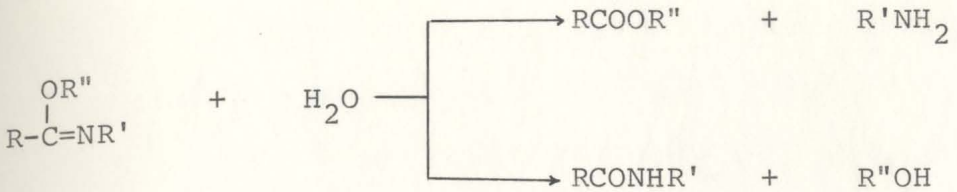
Isolation of formimino-ethers has been attempted by column chromatography, solvent extraction, recrystallisation and sublimation under vacuum; none of these methods was satisfactory because the compounds were always contaminated with the corresponding formanilide and N-alkylformanilide or else underwent hydrolysis before the separation could be achieved. However, pure formimino-ethers were obtainable from preparative gas chromatography, followed by sublimation under vacuum.

DISCUSSION

I. General

Studying the alkylation of amide anions requires determination of the product composition. The effects of changes in reaction conditions are interpreted from changes in the distribution of the different isomers produced. Usually, with ambident anions, it is factors such as cation, solvent, alkylating agent, etc., which affect the site of reaction and the rate of formation of the products. Only the determination for products arising from kinetically controlled reactions is of significance. However, some reaction products tend to rearrange to thermodynamically more stable isomers and, as a result, an equilibrium mixture is obtained. The rearrangements can be thermal, catalysed by the alkylating agent or other reactants or products, etc.. Decomposition of an alkylation product is not uncommon and frequently the starting material is recovered.

In the alkylation of formanilide salts, the alkylation products are N-alkylformanilides and N-phenyl-formiminoalkyl ethers. The former are stable whereas the latter are sensitive to moisture. Although there are two possible pathways for hydrolysis of imino-ethers (Eqn. 7) (22), only the decomposition into starting amide and an alcohol was observed in our reaction. The other pathway is, at most, of minor importance.



(Eqn. 7)

Of the four solvents used, we found that the O-benzylation products from the silver salts underwent partial hydrolysis into starting formanilides and the benzyl alcohols to a greater extent in DMF than in the other solvents, even when the DMF was dried and handled carefully. This could due to the presence of residual water in the DMF and the hygroscopic property of the anhydrous solvent. The hydrolysis of the formimino-ethers occurring in nonpolar solvents such as hexane possibly arises from the water molecules strongly adsorbed by the silver salts and hence not removable.

When an equimolar quantity of water was added to the DMF in the reaction of silver formanilide with benzyl bromide, all the O-alkylation product was decomposed and none was detectable (p. 49). Since no or very little formanilide was observed in control reactions with very carefully dried solvent, glassware and reactants, it is safe to conclude that the formanilide observed in the reaction was from hydrolysis of formimino-ether and not from the contaminating formanilide in the silver salt. Because partial hydrolysis always occurs in the reaction, the actual amount

of formimino-ethers was estimated by converting the formanilides into equivalent amounts of O-alkylation product and adding this to the amount of formimino-ethers that was still present.

Besides their reactivity towards water, rearrangements of formimino-ethers affected by exterior factors must also be considered. The conversion of the imino- into the amido-group is a well known phenomenon and has been extensively studied by G. D. Lander (23) and A. W. Chapman (24). This transformation is found to occur under the catalytic influence of alkyl iodides, but also appears to take place by simple heating. No observable rearrangement of formimino-ethers was found under the alkylation conditions. The amount of N-benzylformanilide from reactions in DMF was not increased on standing (p. 48) and no transformation was seen on refluxing a mixture of N-phenylformiminobenzyl ether and N-benzylformanilide in hexane overnight even in the presence of benzyl bromide (p. 48). In addition, the amount of N-benzylformanilide from the reaction of silver formanilide in DMF to which O-alkylation product had been added was not increased as compared to a reaction conducted under similar conditions (p. 48). Thus, it can be assumed that the product mixture arises from kinetically controlled reactions rather than from a thermodynamic equilibrium. Several formimino-ethers obtained in this work are sufficiently thermally stable to be separated and collected on a vapor phase chromatograph without contamination by the amide isomers.

In addition to the small amounts of starting formanilides and benzyl alcohols appearing in the alkylation products of silver salts, no other by-products were found in most of the reactions. The exception was the alkylation of lithium or potassium formanilide in DMF with p-nitrobenzyl bromide in which a dark red solution resulted when a solution of the alkyl halide in DMF was dropped in. A yellow crystalline material that decomposed above 250°C was also obtained. This indicates an unknown reaction other than alkylation might have taken place and could account for the low yields observed (Table 7).

In the alkylation of the silver salts where formimino-ethers and N-alkylated formanilides were always produced, establishment of a correlation between the amounts of oxygen and nitrogen alkylation and factors such as solvent polarity, the carbonium ion character of the alkyl halide, etc. has been attempted. Unexpectedly, neither a general trend between the O/N values and the properties of solvents and alkylating agents could be established, nor were the results reproducible. When duplicate reactions were done, the values of the ratio of oxygen alkylation to nitrogen alkylation were always scattered over a certain range from run to run. For example, O/N values for the alkylation of silver formanilide from three different batches of the salt in each of the solvents were: in hexane, 8.0, 16.7, 14.3; in toluene, 8.3, 23.4, - ; in DME, 16.3,

33.0, 21.5 and in DMF, 1.4, 4.4, 6.0 (see Table 1). The irreproducibility of the O/N values could result from the partial hydrolysis of formimino-ethers that takes place especially in DMF. Also the accuracy of the estimation of the very small amounts of N-alkylation product could greatly affect the O/N ratio because of the comparatively very large quantity of O-alkylation product. This was the case when DME was the solvent. Thus, other than saying that the highest O-alkylation is obtained from DME, the O/N value is of little quantitative significance. Although the quantity of hydrolysed O-alkylation products has always been estimated and the actual amount corrected, constant O/N values still could not be obtained even in DMF where the amounts of oxygen and nitrogen alkylation were more comparable. Apparently other factors such as heterogeneity of reaction, fineness of silver salts, success in drying the salt, solvent and glassware, etc., could have played some role in the reactions.

II. Effect of Cation

It is well known that in the amide alkylation, the alkali-metal salts favor N-alkylation while the silver salts favor O-alkylation (11 - 14). Of the three different metallic salts of formanilides studied, the lithium and potassium salts were found to react solely on nitrogen and the silver salts to react predominantly on oxygen. These findings are in line with the earlier conclusions.

The tendency for N-alkylation of lithium and potassium formanilides is unaffected by changes in other factors (Tables 5 - 7) whereas the sites of alkylation of silver formanilides are sometimes influenced by the variation of solvent and alkylating agent (Tables 8 - 10). Exceptional cases have been found where silver formanilide alkylation gave predominantly N-alkylation product. These will be discussed later.

The reason the reaction is greatly favored at one site or the other depending on the type of counter cation has not been well explained. Kornblum (1) stressed that the change from nitrogen to oxygen alkylation when the salt is changed from sodium to silver formanilide is due to enhancement of the degree of carbonium ion character in the transition state and the higher negativity of the oxygen atom. This generalisation is not found in the alkylation of formamide with triphenylmethyl chloride and diphenylmethyl chloride (21). These two halides can form relatively stable carbonium ions, yet no alkylation takes place on the more negative oxygen. Furthermore, with p-methoxybenzyl chloride and bromide, no O-alkylation was observed in reaction with silver formanilide (Table 10) although the benzyl carbonium ion is stabilised and the "S_N1" character more obvious.

In the light of the different sites of substitution, counter ions such as lithium, potassium, and tetraethylammonium cations can be regarded as a group that leads to N-alkylation

while silver ion leads to O-alkylation. According to the classification for hard and soft acids and bases (25), lithium and potassium ions are considered to be hard acids and the silver ion to be soft. Similarly, oxygen is a hard base as compared to the softer nitrogen. In the lithium and potassium formanilides, the metal ions tend to associate with the harder nucleophilic center, oxygen, rather than with the softer center, nitrogen, leaving the nitrogen free to react with benzyl halide to give an N-alkylated product. In the same way, the coordination of silver ion with the softer center nitrogen is expected to be more important, and O-alkylation results.

The effect of the coordination existing between the metal ion and the formanilide anion is also revealed in the ease of reaction. Stronger coordination in the lithium salt is reflected by its sluggish reaction compared to the corresponding potassium salt which reacts smoothly under the same conditions.

III. Effect of Solvent

Solvent effects on product distribution in alkylations of lithium and potassium formanilides were not observed, but the reaction rates were enhanced when the better ion solvating solvents were used. Nitrogen is the only site that is attacked in the lithium and potassium salt alkylations in all solvents. On the other hand, the product

distribution in silver salt alkylations depends to some extent on the solvent chosen. The reaction rates of lithium and potassium salts are always in correlation with their solubilities in the solvents. The solubility, and hence the reaction rate, is increased when the metal ion is changed from lithium to potassium and the solvent from hexane, toluene to DME and DMF. Reactions in hexane and toluene are under heterogeneous conditions owing to the small solubilities of lithium and potassium salts in nonpolar hexane and toluene. In DME, only the potassium salts are completely soluble (~2.5M) while in DMF, both lithium and potassium salts form homogeneous solutions and the reactions occur immediately with the deposition of alkali metal halides when the benzyl halides are added. Solutions of lithium salts in DME and DMF are colorless, but the solutions of potassium salts in DME are light green and in DMF are darker, possibly due to traces of potassium metal remaining from the preparation of the potassium salt.

It has been pointed out that the favoring of N-alkylation in lithium and potassium salts is probably due to the metal ion blocking access to the oxygen atom. This could be the case if the substitution takes place on ion aggregates or tightly associated ion pairs. But, in such a strong ion-solvating solvent as DMF, at least part of the potassium formanilide would dissociate and both negative centers, oxygen and nitrogen, would be open to attack by the alkylating agent.

The fact that attack is completely on nitrogen rather than on the more negative oxygen may be explained on the basis of Hammond's postulate (26). Since the transition state possesses both the characteristics of the formanilide anion and of the product and since the N-alkylation product is more stable than the O-isomer, we would expect the activation energy for the transition state leading to O-alkylation to be higher than that leading to N-alkylation product. Thus, the reaction proceeds by the more favorable less energetic path and the more stable N-alkylation product is formed at the faster rate. The exclusively N-alkylation with tetraethylammonium formanilide in DMF lends support to these arguments since dissociation here would be greater than with the potassium or lithium salts.

Although reproducible O/N values could not be obtained in silver salt alkylations, the fact that the highest O/N values tended to arise in DME, intermediate values in hexane, toluene, and smallest values in DMF (Table 1) was distinguishable. Solvent effects were also found in the alkylation of silver salts with benzyl iodide as the alkylating agent. Here, N-alkylation predominated in hexane and toluene.

The N-alkylation resulting from the use of benzyl iodide in hexane and toluene and the larger amount of N-alkylated product obtained with benzyl bromide in the same solvents compared to that in DME probably indicates a direct exchange mechanism has taken place. This will be discussed later.

For alkylation of the silver salts in DMF, the reasoning used to explain N-alkylation of potassium salts in this solvent may be applied to account for the small O/N value. Because in DMF, some of the silver salts will have dissociated, the reaction may also occur in the solution phase, giving N-alkylation product. Similar cases were found in the alkylation of the silver salt of 2-pyridone (8), with oxygen alkylation predominating in nonpolar solvent and nitrogen in polar solvent. The oxygen alkylation has been explained as resulting from a heterogeneous reaction specific to the silver salt and the nitrogen alkylation as due to reaction that takes place in solution. In DME, the solvating power of the solvent is not great enough to dissociate the ion-aggregates of the silver salt but because the solvent is more polar than hexane and toluene, direct exchange of halide (see "Effect of Alkylating Agent") does not occur to any significant extent. The "blocking effect" is thus important and O-alkylation is strongly favored.

It was found that with small amounts of water added to the reaction mixture of silver formanilide in DMF, the amount of N-alkylation was double that from similar reactions conducted under anhydrous conditions (p. 49). This increase in N-alkylation was not seen in DME with water added to the reaction mixture (p. 49). One possible explanation to this phenomenon is that solvent sorting has occurred in the reaction in DMF. Traces of water in DMF can enhance the

rate of entry of the silver salt into the solution phase. As a result more of the reaction occurs in solution to produce more N-alkylation product. With DME, the silver salt should be less soluble and even if some of the salt is solvated by water molecules, the effective concentration of dissolved material is still too low to lead to significant changes in O/N ratio. The effect of added water will not be so pronounced as in DMF.

IV. Effect of Alkylating Agent

A number of different benzyl halides have been employed in the alkylation of lithium and potassium salts yet no shift from nitrogen to oxygen alkylation was found. The product distribution on employing p-methyl- or p-bromobenzyl bromide in silver formanilide alkylations in all solvents are analogous to those with benzyl bromide, i.e. the highest O/N value is always obtained from DME and comparatively more N-alkylation from DMF (Table 10).

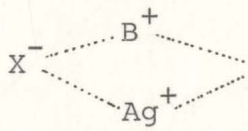
Compared to other alkyl halides, benzyl chloride is very unreactive towards the silver salt; no appreciable reaction was observed in the alkylation of silver formanilide in hexane, toluene, DME and DMF on standing for up to three weeks (Table 10). The reactivity of benzyl chloride to the silver salt is enhanced by introducing an electron donating group on the para position of the halide. A range of 25 - 40% yield was obtained from reactions of silver formanilide with

p-methoxybenzyl chloride in the four solvents (Table 10) while no alkylation was found in a similar reaction with benzyl chloride. When the metal counter ion is the potassium ion, the formanilide salt reacts very well with benzyl chloride in DMF. It gave a 97.7% yield of N-alkylated product on standing for two days at room temperature. Again this is ascribed to the strong solvating power of DMF. Potassium formanilide in this solvent will be more dissociated and the attack on the alkylating agent by the free anion is facilitated.

It has been mentioned previously the reaction of silver formanilides with benzyl iodide in hexane and toluene leads majorly to N-alkylation (O/N ratios 0.1 and 0.6 respectively for the two solvents) and there is comparatively more N-alkylation in hexane and toluene than in DME when benzyl bromide is used (O/N values for one set in the three solvents 16.7, 23.4 and 33.0 respectively). In the former case, it was at first thought possible that contamination of the alkylating agent by iodine due to decomposition of the benzyl iodide might change the mechanism of reaction and cause N-alkylation. Upon comparing a series of trials done under similar conditions but with 1 mg of iodine added to the benzyl bromide and iodide for some of the reactions (Table 8, 9), no obvious change in the results was observed and the possible effect by iodine must be excluded.

The mechanism postulated by Hughes and Ingold (27) which involves the formation of a quadrupole to explain the exchange reaction between triphenylmethyl chloride and salt, is useful to account for the N-alkylation of silver salts in nonpolar solvents. It is possible that a four-center species (quadrupole) is formed analogously from a benzyl halide (BX) and a silver formanilide salt (Ag^+A^-) in hexane and toluene with the reaction scheme drawn as follows:

$$BX \rightleftharpoons B^+X^- \xrightleftharpoons{Ag^+A^-} (B^+X^-)(Ag^+A^-) \rightleftharpoons$$



$$\rightleftharpoons (X^-Ag^+)(B^+A^-) \longrightarrow AB + AgX$$

Ag^+A^- denotes the silver salt of formanilides with the silver ion closely coordinated to one of the negative centers, nitrogen as we have stated before. The quadrupole, after subsequent exchange for silver ion by the benzyl carbonium ion, decomposes into N-alkylated product and silver halide. The reason this is not found or is much less important with benzyl bromide is that the extent of polarization of carbon-halogen bond is greater in benzyl iodide than in benzyl bromide. In addition, the interaction of silver ion with iodide is stronger than with bromide ion. These two factors facilitate the formation of quadrupole from the

benzyl iodide. In polar solvents like DME and DMF, ions and dipoles are less unstable, such quadrupole exchange is less important and benzyl iodide and bromide react similarly.

Other examples of N-alkylation resulting from silver salt are found in the reactions with p-methoxybenzyl chloride and bromide as alkylating agents. The substitutions take place exclusively on nitrogen with yields ranging from 25 to 40%. In neither case was O-alkylation product detected nor were it's hydrolysis products found as they would have been if the imino-ether was present and decomposed. The cause of the low yields is not understood as the purities of the starting materials were reliable. Alkylation on nitrogen may be attributed to the exchange mechanism in hexane and toluene and to reaction in solution in DME and DMF.

In the p-methoxybenzyl chloride and bromide, the polarisation of the carbon-halogen bond is promoted because the developing positive charge on the benzyl group is stabilised not only by delocalization of the charge over the benzene ring, but also by the electron donating effect of the methoxy group on the para position. This promotion of polarization in the carbon-halogen bond greatly facilitates the formation of a quadrupole and N-alkylation results. In DME and DMF, which can effectively solvate cations the passage of amide anion into solution is facilitated by freeing it from coordination with silver ion. Since the

p-methoxybenzyl carbonium ion is stabilised and has a longer life time, the attack by amide anion will be more selective and can take place on more easily polarized center, nitrogen which has the added advantage of leading to the thermodynamically more stable N-benzylated product.

V. Effect of Substituents on Formanilides

No formanilide substituent effect was observed in the alkylation of lithium and potassium salts. The O/N values from silver formanilides with different substituents on the para position alkylated under similar reaction conditions, varied (Table 9) but no correlation between the electronic effects of para substituents and the O/N values could be established. The substituents probably affect the reaction rates much more than they affect the site of alkylation. Cation effects and solvent effects also would override the effects of substituents.

SPECTRA

The IR, NMR, UV and Mass Spectra data of O- and N-alkylated products are summarized in the Table 2 and 3 respectively. Infrared spectra of the N-alkylated products show a strong carbonyl absorption band in the range 1666 - 1675 cm^{-1}, which is the characteristic absorption region of tertiary amides. The formimino-ethers have a strong and sharp absorption band of imino group from 1636 to 1647 cm^{-1}, this is about 20 cm^{-1} lower than the amide absorptions. The difference in absorption position is useful for distinguish of the two groups of compounds. In addition, the absorption appearing in the region 1150 - 1210 cm^{-1}, which indicates the C-O-C stretching, is good confirmatory evidence for the imino-ether linkage in the structures.

The distinctions in the NMR spectra between the two groups of compounds are shown in the methylene and "aldehydic" resonances. Both absorptions are singletsand the spectra do not reveal the presence of stable isomers at room temperature. The methylene absorptions of the amides are usually about 0.3 ppm higher field than those of the imino-ethers whereas the "aldehydic" protons of the former are about 0.8 ppm lower field than those of the latter. The lower τ values of methylene protons of imino-ethers indicate that the methylene groups are attached to the more

Table 2. Spectra of O-alkylated formanilides

R_1	R_2	IR		NMR(τ)[a]			UV(mμ)[b]	Mass spectra (mass unit)	
		C=N cm^{-1}	C-O-C cm^{-1}	H-C=N	$-OCH_2-$	CH_3-	λ_{max}(log ε)	Base peak	Parent peak (%)
H	H	1644	1160-1200	2.29	4.73	-	248(4.17)	91	211(16.57)
H	CH_3	1636	1150-1200	2.23	4.73	7.66	248(4.14)	105	225(13.10)
H	Br	1639	1150-1200	2.20	4.73		220(4.35) 250(sh.)	169 171(98.50)	289(18.80) 291(18.80)
Br	H	1647	1150-1205	2.20	4.69		252(4.03)	91	289(5.55) 291(5.55)
CH_3O	H	1647	1170-1210	2.10	4.67	6.22	250(4.01) 290 295	91	241(71.92)

a. All show singlet absorption, the aromatic protons are multiplet and are not reported.

b. Determined in hexane, measured from 220 mμ.

Table 3. Spectra data of N-alkylated formanilides

R_1	R_2	IR	NMR(τ)[a]			UV mμ[b]	Mass spectra (mass unit)	
		C=O cm^{-1}	H-C=O	$-CH_2-$	CH_3-	λ_{max}(logε)	Base peak	Parent peak (%)
H	H	1666	1.40	4.97	-	233(3.91)	91	211(47.75)
H	CH_3	1666	1.54	5.00	7.68	222(4.01)	105	225(22.80)
H	Br	1669	1.42	5.05	-	225(4.20)	169 171(96.49)	289(39.47) 291(38.60)
H	CH_3O	1669	1.44	5.03	6.26	227(3.98) 285(sh.)		
Br	H	1666	1.42	5.00	-	243(4.23)	91	289(12.75) 291(12.75)
CH_3O	H	1675	1.75	5.06	6.31	230(4.02) 280(sh.)	91	241(60.75)
NO_2	H	1670	1.07	4.85				
H	NO_2	1666	1.32	4.85				

a. All show singlet absorption, the aromatic protons are multiplet and are not reported.

b. Determined in methanol, measured from 220 mμ.

negative oxygens in the compounds and again confirm the ether linkages in the structures.

The UV spectra of the N-alkylated formanilides show strong absorptions from λ_{max} 220 to 240 mμ. The λ_{max} of the imino-ethers are always centered at about 250 mμ, from which the conjugation of a double bond to a benzene ring is inferred.

The mass spectra are relatively simple, both types of compounds have base peaks of tropylium ions arising from the corresponding benzyl groups on the compounds. The parent peaks are strong and usually range from over 10% to 70%, except for the N-benzyl-p-bromoformanilide, which is only 5.5% at an ionization potential of 70 volts.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer as potassium chloride discs (1 - 2 mg sample in 180 mg KCl) for solid samples and as liquid films between sodium chloride plates for liquid samples. Ultraviolet spectra were recorded on a Perkin-Elmer 202 Ultraviolet-Visible spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer using $CDCl_3$ as the solvent with tetramethylsilane as an internal reference. The resonance positions are reported on the τ-scale. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6E mass spectrometer and the spectra were normalized. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. Elemental analyses were determined by Alfred Bernhardt, West Germany.

All solvents were dried thoroughly and distilled under a dry nitrogen atmosphere immediately before use. Hexane and dimethoxyethane (DME) were dried by refluxing over sodium wire for several hours. Toluene was dried similarly and was free from sulfur compounds. Dimethylformamide (DMF) was purified by stirring and heating at about 50^{0}C over calcium hydride for at least 24 hours, followed by fractionating under vacuum.

Formanilide was obtained from Eastman Organic Chemicals. The p-methoxy- and p-bromoformanilides were prepared by treating the corresponding anilines at reflux for 3 - 4 hours with a large excess of formic acid. The excess formic acid was then distilled off and the residue was cooled and allowed to crystallize. The lump was broken into small pieces and washed with cold water until the washings were neutral to litmus. The colorless crystals of the formanilides were obtained after two recrystallisations from aqueous alcohol solution. The purities were checked by determining their melting points.

Benzyl chloride, bromide and iodide were purified by fractionating under vacuum. p-Methoxybenzyl chloride, p-methyl, p-nitrobenzyl bromide were obtained from Eastman Organic Chemicals, p-bromobenzyl bromide, from Aldrich Chemical Co. The last four benzyl halides were used directly without further purification. p-Methoxybenzyl bromide was prepared according to Kornblum (1) and used immediately.

Preparation of Lithium Formanilide

All the glassware was oven heated and all manipulations and reactions were conducted under a slight positive pressure of dry nitrogen. Into a 500 ml three-necked round bottom flask equipped with a condenser, 12.7 g (0.105 mole, 5% in excess to LiH) of formanilide was weighed. Two hundred milliliters of DME was distilled into the flask

and, after the formanilide had completely dissolved, 0.794 g (0.100 mole) of lithium hydride was transferred from a sample vial to the reaction vessel. The solution was then stirred with a magnetic stirrer and heated in an oil bath. Evolution of hydrogen started when the temperature reached about 50°C. The hydrogen was allowed to escape through a U tube bubbler which was connected to the nitrogen source and the top of the condenser through a T-tube. The U tube was filled with suitable amount of paraffin oil to serve as an insolation of the system from the air but still to allow the gas to bubble through freely. White solid salt was deposited gradually and the reaction was allowed to proceed at the reflux temperature of the solvent until the evolution of hydrogen ceased. This usually required more than 5 hours. After the reaction was completed, the flask was allowed to cool and the condenser was replaced with a stopper. The flask was transferred to a nitrogen filled dry box and the white lithium salt was collected on a sintered glass funnel by filtering under reduced pressure. The salt was washed with 50 - 100 ml of dry DME and the solid was sucked as dry as possible. It was then transferred to a 250 ml round bottom flask and pumped with warming to remove the solvent residue.

The lithium salts of p-methoxy-, p-bromo-, p-nitroformanilides were prepared by an analogous procedure. Yields normally exceeded 90%.

Preparation of Potassium Formanilide

The procedure was the same as that for the preparation of lithium formanilide except that potassium metal rather than the hydride was used and benzene was used as the solvent because the potassium salt is quite soluble in DME. The potassium metal (0.100 mole) was freshly cut, the layer of hydroxide removed, and immediately dropped into the reaction flask. The formanilide (0.105 mole) was again in 5% excess. The reaction proceeded rapidly when the potassium metal started to fuse. The potassium formanilide was a fine, light powder and was slightly colored.

The potassium salts of the other formanilides were prepared in a similar way. Over 90% yields were obtained in the preparation of the potassium salts of the formanilides.

Analyses of Lithium and Potassium Formanilides

Neutralization equivalents of the lithium and potassium salts were determined by titrating with standard hydrochloric acid to phenolphthalein end point. The data from titrations and the theoretical neutralization equivalents were as follows: lithium formanilide 122.7, 127.1; potassium formanilide 162.9, 159.2; lithium p-methoxyformanilide 145.8, 157.1; potassium p-methoxyformanilide 193.4, 189.3; lithium p-bromoformanilide 210.6, 205.8; potassium p-bromoformanilide 256.7, 238.0.

The preparation of lithium and potassium salts of higher purity was not attempted since there was no observable change in the alkylation results under different reaction conditions.

Preparation of Silver Formanilides

Silver formanilide was prepared and collected in the dark according to W. J. Comstock and F. Kleeberg (14). All other silver salts were prepared similarly with over 90% of yields. The silver salts were protected from light by wrapping the container with aluminium foil and were dried over phosphorus pentoxide in a vacuum dessicator. The purity was checked by igniting a sample of silver salt, weighing from 0.5 to 0.7 g, in a porcelain crucible to decompose the organic component. The residue, which was nearly pure silver metal, was dissolved in dilute (3N) nitric acid, the carbon residue was removed by filtration and the silver was determined as the silver chloride. The silver contents determined and the theoretical silver contents were: silver formanilide 45.99%, 47.34%; silver p-methoxy-formanilide 41.78%, 40.88%; silver p-bromoformanilide 35.16%, 34.57%.

General Alkylation Procedure

All the transfers were done in a nitrogen filled dry box. About 0.01 - 0.02 mole of the anilide salt was

weighed into a 100 ml round bottom flask and 40 - 50 ml of solvent was added. The alkylating agent, 5% in excess to the anilide salt, was dropped from a dropping pipette into the reaction vessel with swirling. In the case of a solid alkylating agent, it was dissolved in a small amount of the solvent and added in the same way. The flask was stoppered and kept in the dry box. When necessary, the solution were heated to initiate the reactions.

Alkylation of the silver salts was conducted in the same way except the lumps of silver salts were ground into fine particles and precaution was taken to prevent exposure to light. Material from the same batch of the silver salt was always used for the runs with the same alkylating agents in the four different solvents. Heating was avoided for alkylation of the silver salt since the reaction normally proceeded fairly well at room temperature. In addition, the imino-ether, which is the major product, has been reported to be thermally unstable (23).

Preparation and Reaction of Tetraethylammonium Formanilide

In the alkylation of tetraethylammonium formanilide, the salt was prepared by treating 5.43 g (0.023 mole) of silver formanilide with 3.95 g (0.023 mole) of tetraethylammonium chloride in 60 ml of dry DME, with stirring, for three days. The reaction mixture was filtered and the precipitate discarded. The solvent was removed from the filtrate by distilling at

28°C under vacuum. Forty milliliters of freshly distilled DMF was added to the residue and 4.08 g (0.023 mole) of benzyl bromide was dropped in slowly. Reaction started immediately with the deposition of white precipitate. After standing for three hours, the DMF was distilled at 20°C, the residue extracted with 40 ml of benzene and the precipitate filtered and washed with a further 10 ml of benzene. The filtrate was combined and analysis (see below) showed 4.11 g (81.7%) of N-alkylated product was formed.

Determination of Alkylation Products

The reaction solution was filtered with a Büchner funnel under reduced pressure. The inorganic halide and the unreacted salt was washed with a few mls of the solvent and the combined volume of the solution was measured. In cases where hexane was used as solvent, the solid was washed with toluene to ensure complete solution of the organic meterials. When necessary, filter aid was employed to retard the passage of fine particles in the filtration. The filtrate was subject to vpc analysis immediately after filtration.

Vapor phase chromatographic analyses were determined on an Aerograph Model 1520 gas chromatograph by using a thermal conductivity detector. The column packing consisted of 60 - 80 mesh Chromosorb G which had been coated with 1.5 % by weight of OV-17. Ten-foot stainless steel columns (1/8 in. o.d.) containing this packing were used throughout

except that in the analyses of products containing p-bromo- and p-nitro-substituents where pyrolysis tended to occur, a six-foot column was used. The gas chromatograph was operated at 46 ml/min of helium flow and 150 mamp. of filament current with the column oven temperature as shown in Table 4. The temperatures of the injector and detector were usually 10°C higher than the oven temperatures. Retention times of starting formanilides and O- and N-alkylated products are indicated in the same table. Benzyl halides always eluted immediately after the solvent peak. Very small peaks of probably the sec. amines were occasionally found and were neglected.

Table 4. Oven temperatures, retention times of starting formanilides, O- and N-alkylated products

R_1[a]	R_2[b]	Oven temp. °C	Retention times (min.)		
			Formanilide	O-Alkylation product	N-Alkylation product
H	H	227	1.0	2.4	3.6
H	CH_3O	255	0.4	-	3.5
H	CH_3	255	0.5	2.3	3.4
H	Br	254	0.4	2.6	3.7
H	NO_2				
CH_3O	H	254	1.0	2.6	3.7
Br	H	257	1.2	2.6	3.6
NO_2	H				

a. Para substituent on the formanilide.
b. Para substituent on the benzyl halide.

The gas chromatograph was calibrated for all quantitative analyses. Solutions of different known concentrations of the compounds were prepared and constant volumes (5 µl) of these standard solutions were chromatographed. The peak area values from the readings of the disc integrator were then plotted against the concentrations of the samples injected. The calibration curves were straight lines and the results were interpreted graphically. The calibration curves for the N-benzylformanilides were employed to estimate the corresponding formimino-ethers since the responses of the detector to the two isomers were nearly the same. The ratios of peak area per unit mass of O- to N-benzylation products were: N-phenylformiminobenzyl ether to N-benzylformanilide, 1.04; N-p-methoxyphenylformiminobenzyl ether to N-benzyl-p-methoxyformanilide, 1.03; N-p-bromophenylformiminobenzyl ether to N-benzyl-p-bromoformanilide, 1.01; and N-phenylformimino-p-bromobenzyl ether to N-p-bromobenzylformanilide, 0.98. The formanilide peaks appearing in the vpc analyses were also compared with the peak areas of standards. The yields and the product distributions for different reactions are listed in the Tables 5 - 10.

Test for Rearrangement of N-Phenylformiminobenzyl Ether

Into each of two flasks containing 5.70 g (0.025 mole) of silver formanilide, 50 ml of DMF was transferred. To one of the reaction flasks, 1.70 g of N-phenylformiminobenzyl ether

Table 5. Reactions of lithium and potassium formanilides with benzyl bromide

p-R_1-Formanilide Salt		Solvent	Reaction conditions[a]	Percentage yield
R_1	Cation			
H	Li	Hexane	Refluxed 3½ hrs.	4.8
H	Li	Toluene	Refluxed 3½ hrs.	2.1
H	Li	DME	Refluxed 2 hrs.	94.6
H	Li	DMF	20 hrs.	77.0
H	K	Hexane	20 hrs.	85.3
H	K	Toluene	20 hrs.	94.8
H	K	DME	20 hrs.	93.5
H	K	DMF	20 hrs.	95.7
CH_3O	Li	Hexane	No reaction 24 hrs.	4.6
CH_3O	Li	Tolene	refluxed overnight	6.0
CH_3O	Li	DME	Refluxed 45 mins.	72.6
CH_3O	Li	DMF	48 hrs.	74.1
CH_3O	K	Hexane	20 hrs.	77.0
CH_3O	K	Toluene	20 hrs.	78.2
CH_3O	K	DME	20 hrs.	67.2
CH_3O	K	DMF	20 hrs.	65.4
Br	Li	Hexane	Refluxed 19 hrs.	4.3
Br	Li	Toluene	Refluxed 19 hrs.	82.2
Br	Li	DME	No reaction 6 hrs. refluxed 15 mins.	92.1
Br	Li	DMF	48 hrs.	86.3
Br	K	Hexane	40 hrs.	46.0
Br	K	Toluene	40 hrs.	63.0
Br	K	DME	40 hrs.	95.0
Br	K	DMF	40 hrs.	96.0

a. Unless otherwise stated, all reactions were conducted at room temperature (about 22°C).

b. The yield of N-alkylation product.

Table 6. Reaction of lithium and potassium formanilides with benzyl iodide

p-R_1-Formanilide Salt		Solvent	Reaction conditions[a]	Percentag yield
R_1	Cation			
H	Li	DME	Stood overnight, refluxed 1 hr.	87.0
H	Li	DMF	1 day	81.2
H	K	DME	1 day	93.8
H	K	DMF	1 day	93.3
CH_3O	Li	DME	Refluxed 3 hrs.	64.1
CH_3O	Li	DMF	3 days	83.1
CH_3O	K	DME	3 days	87.9
CH_3O	K	DMF	3 days	78.3
NO_2	Li	DME	4 days	35.7
NO_2	Li	DMF	4 days	50.1
NO_2	K	DME	4 days	92.4
NO_2	K	DMF	4 days	64.4
Br	Li	DME	4 days	88.4
Br	Li	DMF	4 days	97.4
Br	K	DME	4 days	91.8
Br	K	DMF	4 days	81.7

a. Room temperature (about 22°C) unless otherwise stated.

b. N-Alkylation product.

Table 7. Reaction of lithium and potassium salts of formanilide with different benzyl halides

Cation	p-R_2-$C_6H_4CH_2X$		Solvent	Duration days[a]	Percentage yield[b]
	R_2	X			
Li	Br	Br	DME	7	88.1
Li	Br	Br	DMF	7	97.7
K	Br	Br	DME	7	97.7
K	Br	Br	DMF	7	97.5
Li	NO_2	Br	DME	6	88.1
Li[c]	NO_2	Br	DMF	6	39.3
K	NO_2	Br	DME	6	74.2
K[c]	NO_2	Br	DMF	6	32.6
Li	CH_3O	Br	DMF	3	93.9
K	CH_3O	Br	DME	3	98.9
K	CH_3O	Br	DMF	3	91.3
Li	CH_3O	Cl	DMF	3	96.3
K	CH_3O	Cl	DME	3	88.3
K	CH_3O	Cl	DMF	3	90.4
K	H	Cl	DMF	2	97.7

a. Room temperature (about 22°C).

b. N-Alkylation product.

c. Duplicate reactions were done and the results were the same. A dark red coloration resulted when the alkylating agent in DMF was dropped in. Besides N-p-nitrobenzylformanilide, yellow crystals decomposing at over 250°C were also obtained.

Table 8. Reaction of silver formanilides with benzyl bromide

p-R_1-Formanilide	Solvent	Duration[a] days	O-Alkylation[b]			Percentage[c] yield
R_1			N-Alkylation			
H[d]	Hexane	2	8	14.3	16.7	73.9
H[e]	Hexane	2	7.9			57.5
H[d]	Toluene	2	8.3	-	23.4	79.1
H[e]	Toluene	2	8.6			91.9
H[d]	DME	2	16.3	21.5	33.0	78.6
H[e]	DME	2	17.8			98.5
H	DMF	2	1.4	6.0	4.4	72.5
CH_3O	Hexane	2	3.7	3.4		77.8
CH_3O	Toluene	2	12.2	19.7		67.0
CH_3O	DME	2	8.8	17		57.6
CH_3O	DMF	2	1.0	3.5		61.4
Br	Hexane	3	1.3	4.4		81.6
Br	Toluene	3	6.0	8.0		77.3
Br	DME	3	10.1	13.5		88.1
Br	DMF	3	0.5	1.0		76.8

a. Room temperature (about 22°C).

b. Numbers in the last two columns are from duplicate runs with same batch of salt under similar conditions, the yields were not determined.

c. Overall yield of O- and N-alkylation products from the first O/N column.

d, e. Parallel reactions but with 1 mg of iodine added to e.

Table 9. Reaction of silver formanilides with benzyl iodide

p-R_1-Formanilide	Solvent	Duration[a] days	O-Alkylation / N-Alkylation	Percentage[b] yield
R_1				
H	Hexane	3	0.07	74.6
H[c]	Hexane	3	0.15	58.2
H[d]	Hexane	3	0.2	81.4
H[c]	Toluene	3	0.6	82.5
H[d]	Toluene	3	0.66	79.8
H	DME	3	20.4	86.3
H[c]	DME	3	14.3	85.6
H[d]	DME	3	14.2	83.9
H	DMF	3	1.3	69.2
CH_3O	Hexane	2	0.36	70.6
CH_3O	Toluene	2	0.63	92.5
CH_3O	DME	2	4.2	94.5
CH_3O	DMF	2	0.8	79.2
Br	Hexane	3	0.04	92.5
Br	Toluene	3	0.3	92.9
Br	DME	3	9.4	85.2
Br	DMF	3	0.87	76.3

a. Room temperature (about 22°C).

b. Overall yield of O- and N-alkylation products.

c,d. Parallel reactions but with 1 mg of iodine added to d.

Table 10. Reaction of silver formanilide with different benzyl halides

p-R_2-$C_6H_4CH_2X$		Solvent	Duration days	O-Alkylation / N-Alkylation	Percentage yield
R_2	X				
CH_3O	Cl	Hexane	5	a	40.8
CH_3O	Cl	Toluene	5	a	24.0
CH_3O	Cl	DME	5	a	32.7
CH_3O	Cl	DMF	5	a	34.3
CH_3O	Br	Hexane	2	a	40.6
CH_3O	Br	Toluene	2	a	35.3
CH_3O	Br	DME	2	a	29.6
CH_3O	Br	DMF	2	a	43.1
Br	Br	Hexane	3	4.8	68.9
Br	Br	Toluene	3	7.0	78.9
Br	Br	DME	3	13.2	82.9
Br	Br	DMF	3	2.0	96.6
CH_3	Br	Hexane	3	10.7	78.9
CH_3	Br	Toluene	3	4.2	74.8
CH_3	Br	DME	3	12.6	78.8
CH_3	Br	DMF	3	1.6	77.8
H[b]	Cl		21	-	-

a. No O-alkylation product was detectable.

b. No observable reactions in all solvents on standing 3 weeks.

was added and 4.20 g (0.025 mole) of benzyl bromide was dropped into both reaction mixtures. The solutions were stirred and allowed to stand for 3 days. The product from the control reaction was found to contain 2.40 g of N-phenylformiminobenzyl ether and 0.66 g of N-benzylformanilide. The reaction which had N-phenylformiminobenzyl ether added contained about the same amount of N-benzylformanilide (0.65 g), while the total amount of the formimino-ether was 4.10 g, which is equal to the sum of the added formimino-ether and the formimino-ether expected from the alkylation reaction, assuming the yields of both reactions were the same. The percentage of conversion was 58. Moreover, the amount of N-benzylformanilide in the product mixture did not show any increase after the precipitate was removed by filtration and the solution was allowed to stand at room temperature for one week.

Also the amount of N-alkylation product was not increased by refluxing overnight a mixture of 2.70 g of N-phenylformiminobenzyl ether and 0.90 g of N-benzyl-formanilide in 60 ml of hexane with 0.50 g of benzyl bromide added.

Test for Sensitivity of N-Phenylformiminobenzyl Ether to Moisture

A series of four reactions were done, each reaction containing 4.50 g (0.02 mole) of silver formanilide in 50 ml

of DMF, to which 2.40 g (0.02 mole) of benzyl bromide was added. The first two reactions were conducted under anhydrous condition whereas the last two with 0.45, 0.90 g of water added respectively. The reaction products were analysed on the gas chromatograph and the relative peak areas of formanilide for the four reactions were 1, 1, 2, 2; N-phenylformiminobenzyl ether 1, 1, 0, 0; and N-benzyl-formanilide 1, 1.2, 2, 2. When analysed at an oven temperature of 137^{0}C, about five times as much benzyl alcohol was found in the last two reactions as the first. Only a very small amount of aniline was detected.

Similar studies in DME with water added did not show any difference from the reactions run in anhydrous conditions except that the amount of formanilide was increased.

A blank of 1.50 g of silver formanilide in 15 ml of DMF was done and no formanilide was found.

Isolation of the N-Alkylation Products

The N-alkylated products were easily obtained from the reaction of the appropriate lithium or potassium formanilides with the benzyl halides. Usually DME was chosen as the solvent for the alkylation reaction and the solution was refluxed for 3 - 4 hours. After the reaction was complete, the DME was stripped off with a flash evaporator and the residue was dissolved in water. The organic material was extracted with ether and the ether extract dried with anhydrous

magnesium sulfate. After two or three recrystallisations from ether, pure N-alkylformanilides were obtained. The melting points and results of elemental analyses are shown in Table 11. Spectral results are summarized in Table 2.

Isolation of the O-Alkylation Products

The crude formimino-ethers were obtained from alkylation of the appropriate silver formanilides in DME. Pure formimino-ethers were collected from the gas chromatograph by using a 8-ft × ¼" o.d. stainless steel or aluminium column packed with same packing material used for analyses. The flow rate of helium was 50 ml/min and the filament current of the detector was decreased from 150 mamp. to 75 - 80 mamp. to reduce decomposition of the compound. The oven temperature was adjusted so that the retention time of each of the components was close to that shown in Table 2. Usually the operating temperature of the oven was within five degrees of that shown in the table. The compound collected, if it was a liquid, was purified by molecular distillation at 65°C under 0.05 mm Hg. Solid compounds were purified by sublimation at a temperature 5°C below their melting points under the same vacuum. The purity of the compounds was checked by determining their melting points and by I.R. spectra where impurities of carbonyl compounds could be detected even if present at low concentrations.

Table 11. Melting points and elemental analyses of O- and N-alkylated products

R_1	R_2[a]	N-Alkylated product		O-Alkylated product		Calculated
		M.P. (°C)	Found	M.P. (°C)	Found	
H	H	48 (lit. 48)		13-14	C : 79.59 H : 6.15 N : 6.56	C : 79.60 H : 6.20 N : 6.62
H	CH_3	45	C : 79.88 H : 6.68 N : 6.19	69	C : 80.11 H : 6.80 N : 6.25	C : 80.00 H : 6.66 N : 6.22
H	CH_3O	69	C : 74.43 H : 6.06 N : 6.00			C : 74.69 H : 6.22 N : 5.81
H	Br	77	C : 57.83 H : 4.15 N : 4.64 Br: 27.57	79-80	C : 57.89 H : 4.33 N : 4.87 Br: 27.34	C : 57.93 H : 4.13 N : 4.83 Br: 27.58
CH_3O	H	48.5-49	C : 74.59 H : 6.11 N : 5.86	80.5	C : 74.55 H : 6.39 N : 5.91	C : 74.69 H : 6.22 N : 5.81
Br	H	61.5	C : 57.72 H : 4.33 N : 4.63 Br: 27.35	71.5-72	C : 57.75 H : 4.20 N : 4.73 Br: 27.53	C : 57.93 H : 4.13 N : 4.83 Br: 27.58
NO_2	H	100				
H	NO_2	100.5-101				

a. R_1 and R_2 are, respectively, the para-substituent on the formanilide and on the benzyl halide used to prepare the particular alkylated formanilide.

REFERENCES

1. N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland. J. Amer. Chem. Soc. 77, 6269 (1955).

2. W. J. LeNoble and H. F. Morris. J. Org. Chem. 34, 1969 (1969) and references there in.

3. N. Kornblum, P. J. Berrigan and W. J. LeNoble. J. Amer. Chem. Soc. 85, 1141 (1963); 82, 1257 (1960).

4. R. Scholl and W. Egerer. Liebigs Ann. Chem. 397, 358, 361 (1913).

5. C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos and C. A. Vander Werf. J. Amer. Chem. Soc. 84, 43 (1962).

6. N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Graham. J. Amer. Chem. Soc. 78, 1497 (1956).

7. P. A. S. Smith and J. E. Robertson. J. Amer. Chem. Soc. 84, 1197 (1962).

8. J. P. Jonak, G. C. Hopkins and H. J. Minnemeyer. J. Org. Chem. 35, 2512 (1970) and references there in. N. M. Chung and H. Tieckelmann. J. Org. Chem. 35, 2517 (1970) and references there in.

9. W. J. LeNoble. Synthesis. No. 1, 1 (1970). R. Gompper. Angew. Chem. Internat. Edit. 3, 560 (1964). S. A. Shevelev. Usp. Khim. 39, 1773 (1970); Chem. Abs. 74, 3131g (1971).

10. B. C. Challis and J. A. Challis in "The Chemistry of Amides", edited by Jacob Zabicky, Interscience, (1970). pp. 731 - 752 and references there in.

11. W. J. Hickinbottom. "Reactions of Organic Compounds", 3rd ed., Longmans, Green and Co., New York, (1957). pp. 409 - 411.

R. Levine and W. C. Fernelius. Chem. Rev. 54, 467 (1954).

12. L. E. Smith and J. Nichols. J. Org. Chem. 6, 502 (1941).

13. G. D. Lander. J. Chem. Soc. 79, 690 (1901).

14. W. J. Comstock and F. Kleeberg. J. Amer. Chem. Soc. 12, 499 (1890).

15. A. Pilotti, A. Reuterhall and K. Torssell. Acta Chem. Scand. 23, 818 (1969) and references there in.

16. W. Hechelhammer. Ger. Pat., 948, 973 (1956).

17. R. Gompper. Chem. Ber. 93, 187, 198 (1960).

J. W. Ralls. J. Org. Chem. 26, 66 (1961).

18. C. J. M. Stirling. J. Chem. Soc. 255 (1960).

19. H. W. Heine, P. Love and J. L. Bove. J. Amer. Chem. Soc. 77, 5420 (1955).

20. H. W. Heine. J. Amer. Chem. Soc. 78, 3708 (1956).

21. H. Bredereck, R. Gompper, H. Rempfer, K. Klemm and H. Keck. Chem. Ber. 92, 329 (1959).

R. Gompper and O. Christmann. Chem. Ber. 92, 1935 (1959).

22. R. H. DeWolfe. J. Org. Chem. 36, 162 (1971).

23. G. D. Lander. J. Chem. Soc. 83, 406 (1903).

24. A. W. Chapman. J. Chem. Soc. 1743 (1927).
J. W. Schulenberg and S. Archer. "Organic Reactions", John Wiley and Sons Inc., New York, Vol. 14. (1965). p. 1.

25. R. G. Pearson. J. Amer. Chem. Soc. 85, 3533 (1963).

26. G. S. Hammond. J. Amer. Chem. Soc. 77, 334 (1955).

27. C. A. Bunton in "Nucleophilic Substitution at a Saturated Carbon Atom". Elsevier, Vol. 1. Edited by E. D. Hughes (1963). p. 138.